(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number
WO 2005/107582 A1

(51) International Patent Classification[7]: A61B 5/02, A61N 1/365

(21) International Application Number: PCT/SE2004/000698

(22) International Filing Date: 6 May 2004 (06.05.2004)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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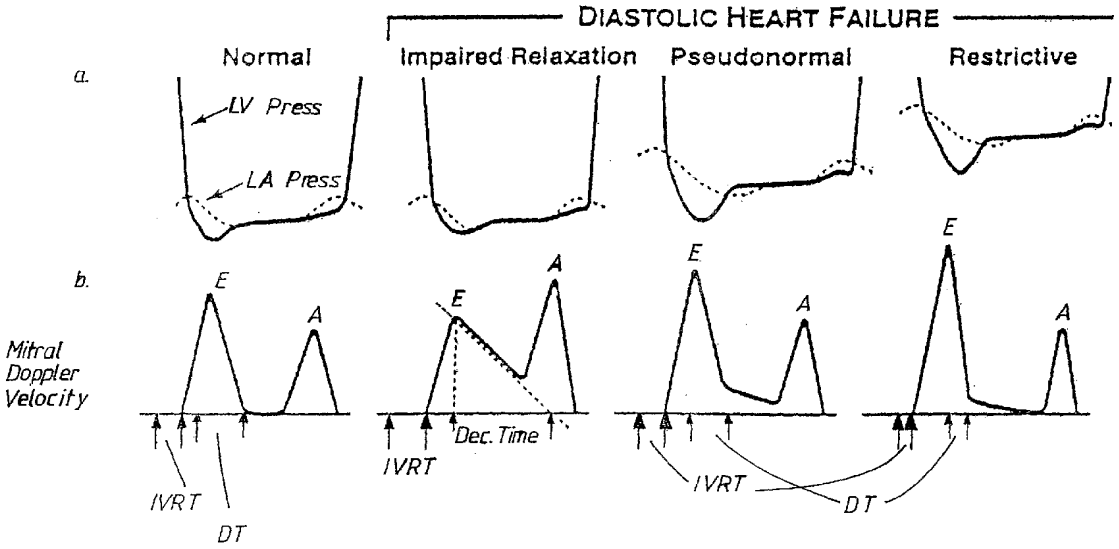
[Continued on next page]

(54) Title: DETECTION OF DIASTOLIC HEART FAILURE



(57) Abstract: An implantable medical apparatus for detecting diastolic heart failure, DHF, comprises a DHF determining device for determining at least one DHF parameter for detecting a DHF state of the heart of a patient. The DHF determining device comprises a means for determining, as said DHF parameter, the time length (DT,IVRT) of a predetermined phase of diastole. A pacemaker comprises such an apparatus and control means for optimising pacing therapy and pacemaker settings depending on the determined time length. A corresponding method of detecting diastolic heart failure, DHF, comprises the step of determining at least one DHF parameter for detecting a DHF state of the heart of a patient. This step comprises determining, as said DHF parameter, the time length (DT,IVRT) of a predetermined phase of diastole.

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EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

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DETECTION OF DIASTOLIC HEART FAILURE

Technical Field

The present invention relates to an implantable medical apparatus for detecting diastolic heart failure, DHF, comprising a DHF determining device for determining at least one DHF parameter for detecting a DHF state of the heart of a patient. The invention also relates to a pacemaker having such an apparatus, and a method for detecting diastolic heart failure, DHF, comprising the step of determining at least one DHF parameter for detecting a DHF state.

Background

There is a growing recognition that congestive heart failure caused by a predominant abnormality in the diastolic function, i.e. diastolic heart failure, DHF, is both common and causes significant morbidity and mortality. Therefore early detection of DHF is important such that a suitable treatment can be started. Patients do not, however, seem to have symptoms at an early stage. In addition it has been hard to separate diastolic and systolic heart failure and they may also exist simultaneously.

The time progress of different phases of diastole of a patient suffering from DHF is changed vis-à-vis that of a healthy person, see Michael R. Zile and Dirk L. Brusaert, "New Concepts in Diastolic Dysfunction and Diastolic Heart Failure: Part I", Circulation 2002; 105: 1387. Thus DHF can be divided into three phases, see figure 1. Figure 1a shows left atrial pressure, LA dotted line, and left ventricular pressure, LV solid line, as functions of time for a normal, healthy state and for three phases of DHF. The first phase of DHF is referred to as "Impaired Relaxation". In this phase characteristic times related to relaxation and filling of the left ventricle is prolonged compared to corresponding times of a normal heart. After this phase the disease progresses into a phase called "Pseudonormal". In this phase the heart compensates and the characteristic times returns to more normal values, close to those of the normal heart. This phase is followed by the final phase of DHF called "Restrictive". In the final phase the characteristic times are shorter than for the normal heart. Figure 1b shows corresponding measured mitral blood flow velocities. Letter "E" denotes the so-called E-wave, early filling of the ventricle, and "A" the A-wave, contribution from the atrium during its contraction.

The purpose of the present invention is to utilize these changes in time during diastole of patients suffering from DHF for proposing a technique for DHF detection.

Disclosure of the Invention

This purpose is obtained by an apparatus, a pacemaker and a method of the kind mentioned in the introductory portion of the description and having the characterizing features of claims 1, 17 and 18 respectively.

Thus with the present invention early detection of DHF is possible and it is also possible to detect how the disease progresses. Even the beginning of a DHF of a healthy person can be detected.

According to advantageous embodiments of the apparatus according to the invention the DHF determining device comprises sensor and calculating means for determining the time, DT, from the occurrence of peak blood flow velocity through the mitral valve to zero blood flow velocity therethrough as said DHF parameter.The sensor and calculating means are adapted to determine DT by extrapolating the mitral blood flow velocity to zero, if zero velocity is not obtained before atrial contraction. The sensor and calculating means are then preferably adapted to determine the time derivative of the blood flow velocity through the mitral valve shortly after said peak blood flow velocity for use for linearly extrapolating the blood flow velocity to zero. DT denotes the E-wave deceleration time or "Dec time" related to the early filling of the left ventricle as mentioned above. If zero velocity is not obtained due to the atrial contraction, so-called A-wave influence, which will be described more in detail below. DT can consequently be determined by extrapolation in such situations.

According to still another advantageous embodiment of the apparatus according to the invention the DHF determining device comprises sensor and calculating means for determining isovolumic relaxation time, IVRT, i.e. the time from the closing of the aortic valve to the opening of the mitralis valve, as said DHF parameter.

According to yet other advantageous embodiments of the apparatus according to the invention the sensor and calculating means comprise a means for measuring IEGM or a means for measuring an impedance in the patient ´s heart or a sound sensor or an accelerometer, intended to be placed on the left ventricle of the patient ´s heart, for determining DT and/or IVRT. Thus e.g. IVRT can be

determined from impedance measurements between the left and right ventricles, or possibly between the left ventricle and right atrium. Since there is no change in the blood volume between electrodes located as indicated above during IVRT the impedance will be substantially constant. IVRT can consequently be identified as a "still" period in the impedance after systole. IVRT can also be determined by an accelerometer positioned on the left ventricle, for instance in one of the coronary veins running on the outside of the left ventricle. IVRT is then determined by the time the ventricle is still after systole, since the ventricle is still during IVRT. No blood enters or leaves the ventricle during this phase of the cardiac cycle, only a redistribution of the pressure takes place within the ventricle without change of volume of the ventricle. DT can be determined by e.g. listening to the blood flow through the mitralis valve. The blood velocity is correlated to the frequency of the heart sound signal, its derivative corresponds to the acceleration of the blood, and DT is calculated therefrom.

According to other advantageous embodiments of the apparatus according to the invention the DHF determining device is adapted to determine the time length at predetermined time intervals and a storing means is provided for storing said determined time lengths. The DHF determining device can alternatively be adapted to determine changes in said time length and a storing means be provided for storing the determined changes in time length. During the follow-up of the patient stored parameters are downloaded from the storing means and evaluated by the physician for studying the progression of the disease It is also possible to provide an alerting means to be triggered if deviations of the determined time length from predetermined limit values exceed a predetermined threshold value, or a change in the determined time length exceeds a predetermined threshold value. Thus in response to the detection of a change in the DHF parameter indicating that the patient is developing DHF or the patient is progressing into a new phase of DHF an alert can be sent calling for a follow-up by a physician.

The invention also relates to a pacemaker provided with the apparatus for detecting DHF and control means for optimising pacing therapy and pacemaker settings depending on the determined time length, as well as a method of detecting DHF.

Brief Description of the Drawings

To explain the invention in greater detail embodiments of the invention will now be described with reference to the drawings on which figure1a and b shows left ventricular and left atrial pressures and mitral blood flow velocity respectively for a normal heart and for three phases of DHF, figures 2 – 4 illustrate impedance measurements for determining IVRT in three embodiments of the invention, figure 5 illustrates an embodiment of the invention comprising special sensors for DT and IVRT determination, and figure 6 is a diagram illustrating when DT and IVRT values are stored for later evaluation and when a DHF alert is sent according to an exemplifying embodiment of the invention.

Description of Preferred Embodiments

Figure 1a shows left ventricular pressure, LV Press solid line, and left atrial pressure, LA Press dotted line, during diastole and figure 1b corresponding mitral Doppler left ventricular blood inflow, as measured by echocardiography, for a normal healthy heart and for three phases of diastole. Normal diastolic function is characterized by a predominant early diastolic mitral flow, E-wave, exceeding the velocity of left ventricular filling contributed by atrial contraction, A-wave in the figure. With impaired relaxation atrial contraction contributes relatively more to ventricular filling, viz. A-wave > E-wave, with prolonged deceleration of the E-wave, usually > 240 msec. This phase of DHF "Impaired Relaxation" is common with increasing age and may identify patients at risk for DHF. When ventricular diastolic pressure increases to the point where atrial contraction contributes little to the filling, the E-wave again becomes predominant but with rapid deceleration, first in a "Pseudonormal" pattern and ultimately in a "Restrictive" pattern, characterized by a high E-wave velocity of usually more than twice the A-wave velocity.

One of the time lengths which can be used to indicate the progress of DHF is the E-wave deceleration time, DT "Dec. Time", see figure 1b. DT is defined as the time length from the point of blood peak velocity through the mitral valve to the point of zero velocity, cf. figure 1b. If zero velocity is not reached due to the A-wave influence, DT is calculated by extrapolation as illustrated in figure 1b for the phase "Impaired Relaxation". The time derivative of the flow velocity through the mitral valve shortly after the blood flow peak velocity is determined for use for linearly

extrapolating the blood flow velocity to zero. By measuring DT the beginning of a DHF and its progress can be detected.

The progress of DHF can be divided into three phases as mentioned above and each of these phases causes a change in DT, see figure 1b. The first phase of DHF is referred to as "Impaired Relaxation". During this phase DT is much longer than in a normal heart. After this phase the disease progresses into a phase called "Pseudonormal". In this phase the heart compensates and DT returns to more normal values, close to the DT value of a normal heart. This phase is followed by the final stage of DHF called "Restrictive" In this phase DT is shorter than DT of a normal healthy heart.

Another time length which can be used to indicate the progress of DHF is the isovolumic relaxation time, IVRT, as mentioned above. In the "Impaired Relaxation" phase of diastole IVRT is longer than for a healthy heart, as appears from figure 1b. In the "Pseudonormal" phase the heart is compensating and IVRT returns to more normal values. In the final "Restrictive" phase IVRT is decreased to a shorter value than IVRT of the normal heart, cf. figure 1b.

A pacemaker according to the invention will preferably use its sensors for determining IEGMs or impedance measurements for measuring and calculating DT or IVRT at given time intervals, as will be described in further details below, and either store DT or IVRT or changes in DT or IVRT in the memory of the pacemaker. In the follow-up the development of DT or IVRT over time is downloaded from the pacemaker and the physician can evaluate the results and study the progression or regression of the disease.

An alerting means can also be provided to send an alert, calling for a follow-up for the patient in question, in response to the detection of a change in DT or IVRT indicating that the patient is developing DHF or the patient is progressing into a new phase of DHF.

IVRT is initiated by the closing of the aortic valve and terminated by the opening of the mitral valve. To determine when the aortic and mitral valves closes and opens respectively impedance measurements or some kind of sensor can be used. Figure 2 illustrates an example of impedance measurements between left and right ventricles 1, 3. A current is supplied between the pacemaker case, schematically shown at 2, and the tip electrode 4 of a right ventricular lead 6, and

the resulting voltage is measured between the ring electrode 8 of the ventricular lead 6 and the tip electrode 10 of a unipolar coronary sinus lead 12.

Figure 3 illustrates an example wherein current is fed between the ring electrode 14 of a bipolar right atrial lead 16 and the ring electrode 20 of a bipolar coronary sinus lead 18, and the resulting voltage is measured between the tip electrodes 22 and 24 of the right atrial lead 16 and the coronary sinus lead 18 respectively.

Figure 4 illustrates still another embodiment wherein current is supplied between the tip electrode 26 of a bipolar right ventricular lead 28 and the ring electrode 30 of a bipolar coronary sinus lead 32, and the resulting voltage is measured between the ring electrode 34 of the right ventricular lead 28 and the tip electrode 36 of the coronary sinus lead 32.

Since there is practically no change in the blood volume during IVRT between the electrodes used in the embodiments illustrated above, the impedance measured in this way is substantially constant. IVRT can consequently be identified as the "still" period in the impedance after systole.

Figure 5 illustrates an embodiment wherein a special sensor 38 is used. This sensor can be of a kind which picks up noise or registers mechanical events, such as for instance a so-called CMES-sensor, cardiac mechanical sensor,. The CMES-sensor is a piezoelectric sensor the output signal of which contains a. o. pressure information. This information comprises several components, and in a certain frequency range the sensor is sensible to noise, i.e. it works as a microphone. The signal from the sensor comprises also the true pressure and its derivative. By suitable filtering of the sensor signal valve openings and closings can be detected.

The sensor 38 in figure 5 can alternatively comprise an accelerometer positioned on the left ventricle, for instance in one of the coronary veins running on the outside of the left ventricle, as shown in the figure. IVRT is then detected as the time when the ventricle is still after systole. During this time no blood leaves or enters the ventricle which consequently does not change volume.

DT can be determined in an analogous way by impedance measurements or by noise measurements with the aid of a microphone positioned in a coronary vein as illustrated in figure 5, or positioned in the right ventricular apex. DT can also

be determined by an accelerometer positioned on the outside of the left side of the heart, i.e. in the coronary sinus.

The time length used as parameter for detection of DHF can also be determined by more than one of the above described techniques.

Typical values of IVRT of a healthy person are 70 – 90 msec depending on age and other parameters, and typical values of DT of a healthy person are 160 – 240 msec. IVRT and DT values above 90 and 240 msec respectively are assumed to characterize a state of impaired relaxation, and values below 70 and 160 msec respectively are characterizing the restrictive phase of DHF. Thus an increase or decrease of IVRT and DT above or below the above mentioned limit values are indications of DHF and should therefore call for attention. This is illustrated in figure 6 which shows that time length values within the normal range are not stored, whereas time length values above or below the prescribed limit values are stored together with their times of occurrence. These measured time length values outside the normal range can also be triggering an alert.

The amount of deviation of the measured time lengths above or below their rspective limit values is an indication of the severity of the DHF.

Thus, if the IVRT and DT values fall outside their respective normal ranges these values are stored together with the amounts by which the time lengths exceed or are below the respective limit. Possible erroneous measurement values are filtered out, such that single or very few time length values outside the normal ranges should not result in a DHF detection, and not trigger a possible alert.

CLAIMS

1. An implantable medical apparatus for detecting diastolic heart failure, DHF, comprising a DHF determining device for determining at least one DHF parameter for detecting a DHF state of the heart of a patient, **characterized in** that said DHF determining device comprises a means (2, 4, 8, 10; 14, 20, 22, 24; 26, 30, 34, 36; 38) for determining, as said DHF parameter, the time length of a predetermined phase of diastole.

2. The apparatus according to claim 1, **characterized in** that comparison means are provided to compare said time length with predetermined upper and lower limit values for the detection of DHF.

3. The apparatus according to claims 1 or 2, **characterized in** that said DHF determining device comprises sensor and calculating means (2, 4, 8, 10; 14, 20, 22, 24; 26, 30, 34, 36; 38) for determining the time, DT, from the occurrence of peak blood flow velocity (E) through the mitral valve to zero blood flow velocity therethrough as said DHF parameter.

4. The apparatus according to claim 3, **characterized in** that said sensor and calculating means are adapted to determine DT by extrapolating the mitral blood flow velocity to zero, if zero velocity is not obtained before atrial contraction.

5. The apparatus according to claim 4, **characterized in** that said sensor and calculating means are adapted to determine the time derivative of the blood flow velocity through the mitral valve shortly after said peak blood flow velocity (E) for use for linearly extrapolating the blood flow velocity to zero.

6. The apparatus according to claim 1 or 2, **characterized in** that said DHF determining device comprises sensor and calculating means (2, 4, 8, 10; 14, 20, 22, 24; 26, 30, 34, 36; 38) for determining isovolumic relaxation time, IVRT, as said DHF parameter.

7. The apparatus according to any of the claims 3 - 6, **characterized in** that said sensor and calculating means comprise a means for measuring IEGM for determining DT and/or IVRT.

8. The apparatus according to any of the claims 3 - 6, **characterized in** that said sensor and calculating means comprise a means (2, 4, 6, 8, 10, 12; 14, 16, 18, 20, 22, 24; 26, 28, 30, 32, 34, 36) for measuring an impedance in the patient ´s heart for determining DT and/or IVRT.

9. The apparatus according to any of the claims 3 - 6, **characterized in** that said sensor and calculating means comprise a sound sensor (38) for determining DT and/or IVRT.

10. The apparatus according to any of the claims 3 - 6, **characterized in** that said sensor and calculating means comprise an accelerometer (38), intended to be placed on the left ventricle of the patient ´s heart, for determining DT and/or IVRT.

11. The apparatus according to any of the preceding claims, **characterized in** that said DHF determining device is adapted to determine said time length at predetermined time intervals and in that a storing means is provided for storing said determined time lengths.

12. The apparatus according to any of the claims 2 - 11, **characterized in** that said comparison means are connected to said storing means for storing said time length values above said upper limit and below said lower limit values together with the magnitudes of the deviations from corresponding limit values and the times of the occurrence of the deviated values.

13. The apparatus according to any of the claims 1 – 10, **characterized in** that said DHF determining device is adapted to determine changes in said time length and in that a storing means is provided for storing said determined changes in time length.

14. The apparatus according to any of the claims 2 – 10, **characterized in** that

an alerting means is provided to be triggered if deviation of the determined time length from said upper or lower limit values exceed a predetermined threshold value.

15. The apparatus according to claim 14, **characterized in** that said alerting means is adapted to be triggered if said time lengths exceed said upper or are below said lower limit for a time period of predetermined length.

16. The apparatus according to any of the claims 1 - 14, **characterized in** that an alerting means is provided to be triggered in response to the detection of a change in said determined time length exceeding a predetermined threshold value.

17 A pacemaker, **characterized in** that it comprises an apparatus according to any one of the preceding claims and control means for optimising pacing therapy and pacemaker settings depending on the determined time length.

18. A method of detecting diastolic heart failure, DHF, comprising the step of determining at least one DHF parameter for detecting a DHF state of the heart of a patient, **characterized in** that said step of determining at least one DHF parameter comprises determining, as said DHF parameter, the time length of a predetermined phase of diastole.

19. The method according to claim 18, **characterized in** that said DHF parameter is the time, DT, from the occurrence of peak blood flow velocity (E) through the mitral valve to zero blood flow velocity therethrough.

20. The method according to claim 19, **characterized in** that to determine DT the mitral blood flow velocity is extrapolated to zero, if zero velocity is not obtained before atrial contraction.

21. The method according to claim 20, **characterized in** that the time derivative of the blood flow velocity through the mitral valve shortly after said blood flow peak velocity (E) is determined for use for linearly extrapolating the blood flow velocity to zero.

22. The method according to claim 18, **characterized in** that said DHF parameter is the isovolymic relaxation time, IVRT,

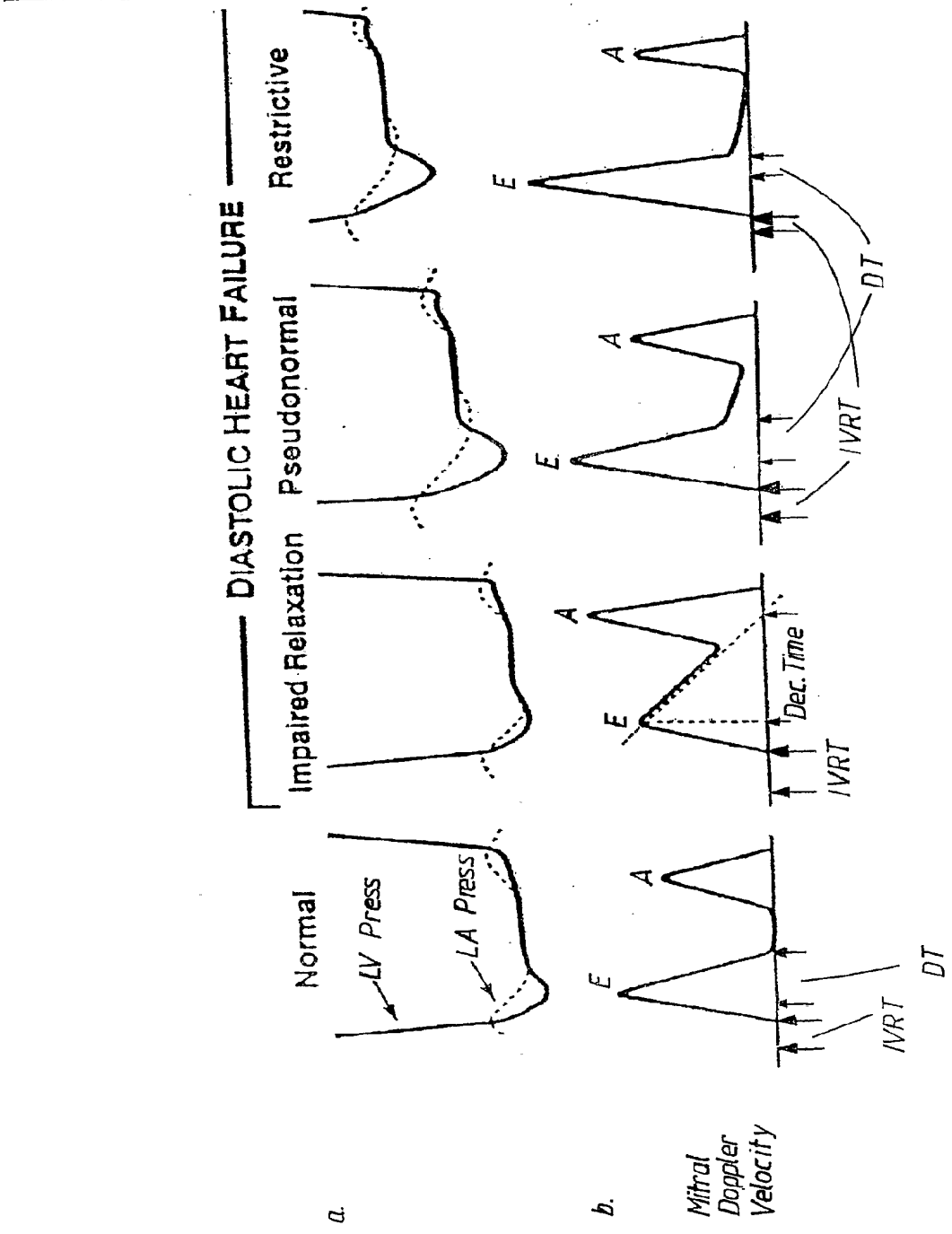
23. The method according to any of the claims 19 – 22, **characterized in** that IEGM is measured for determining DT and/or IVRT.

24. The method according to any of the claims 19 – 23, **characterized in** that an impedance in the patient ´s heart is measured for determining DT and/or IVRT

25. The method according to any of the claims 18 – 24, **characterized in** that said time length is determined at predetermined time intervals and stored.

26. The method according to any of the claims 18 – 24, **characterized in** that changes in said time length are determined and stored.

Fig. 1


DIASTOLIC HEART FAILURE
Normal
Impaired Relaxation
Pseudonormal
Restrictive
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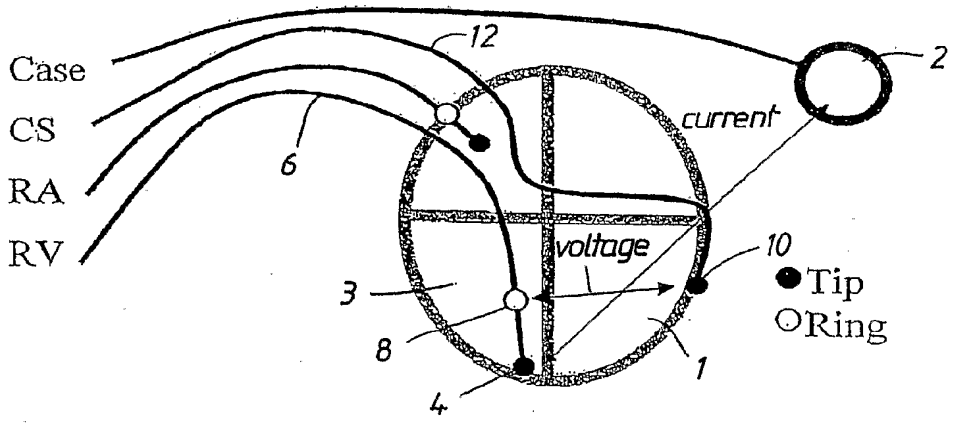
LA Press
a.
b.
E
A
Dec. Time
IVRT
DT
Mitral Doppler Velocity

Fig. 2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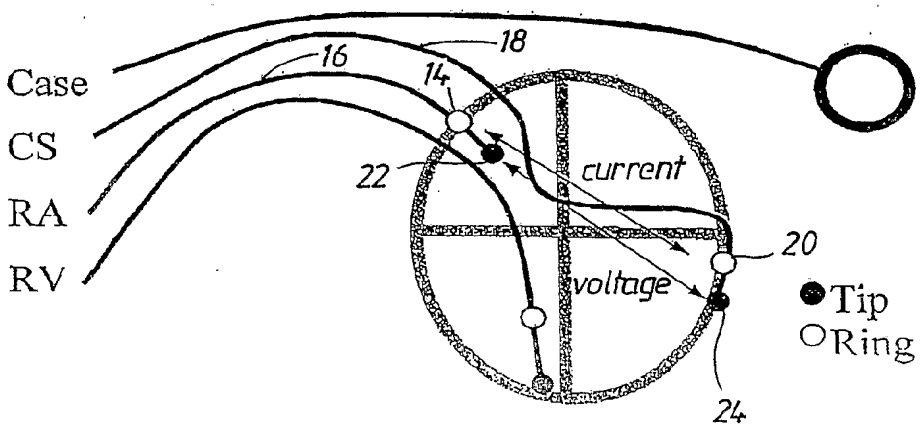
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Fig. 4

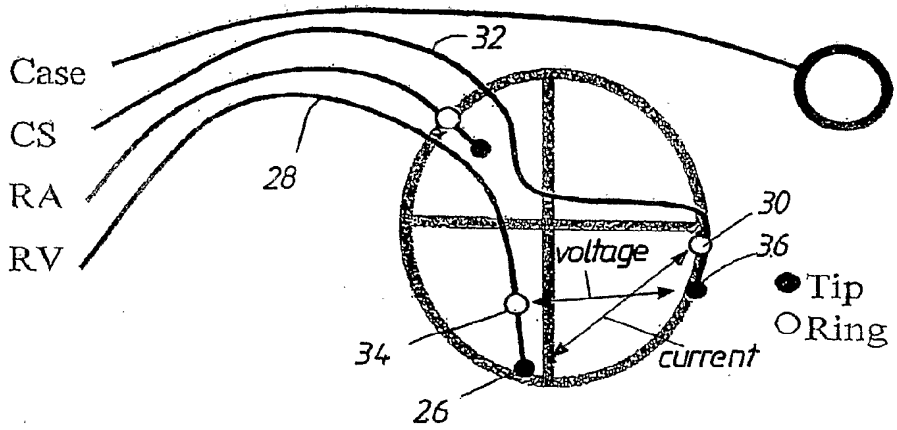
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Fig. 5

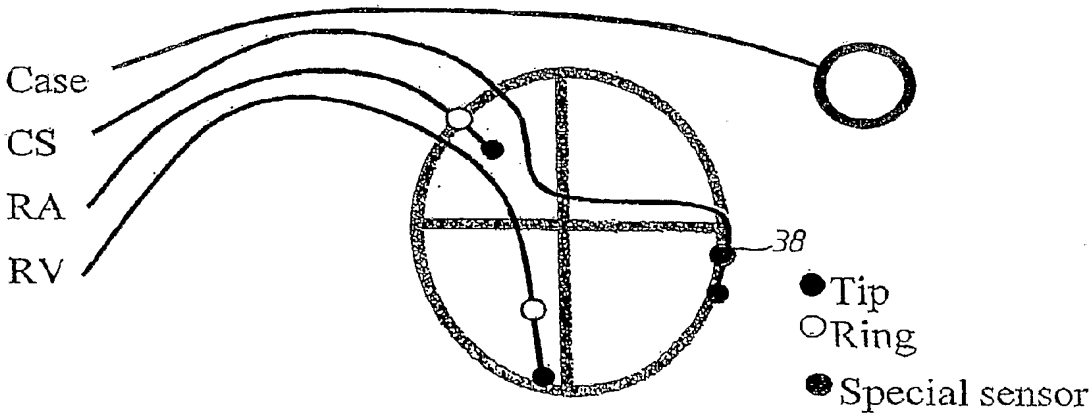
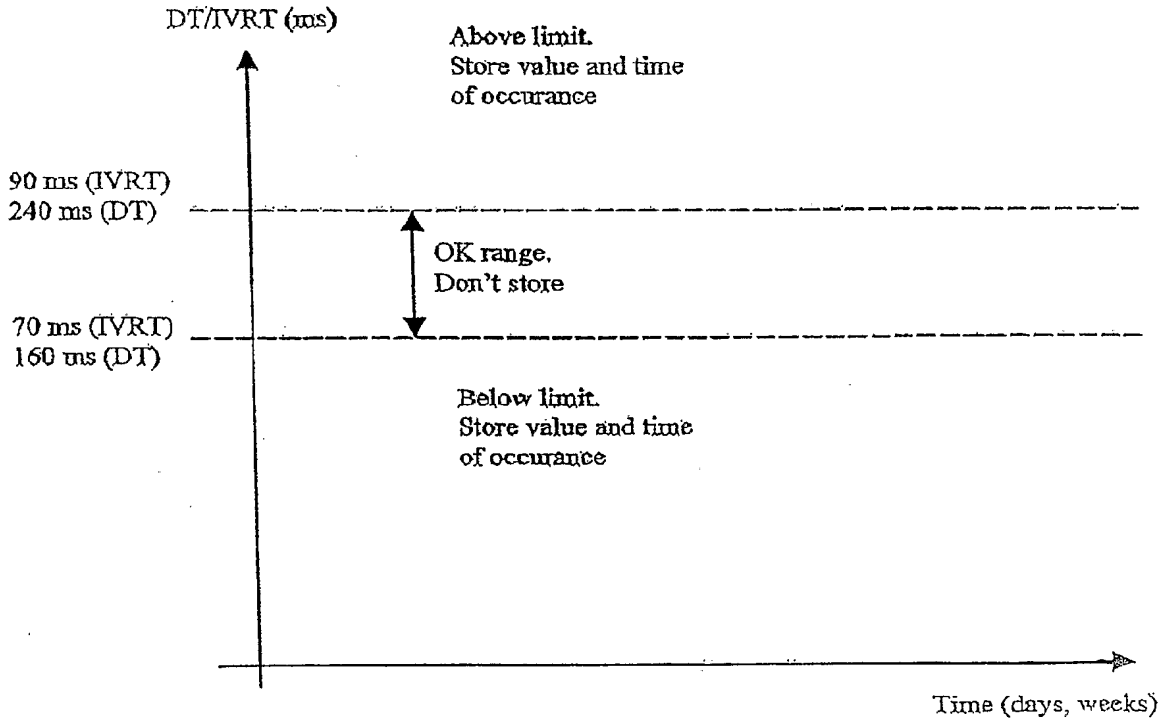

Case
CS
RA
RV
38
Tip
Ring
Special sensor

Fig. 6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Store value and time
of occurance
90 ms (IVRT)
240 ms (DT)
OK range.
Don't store
70 ms (IVRT)
160 ms (DT)
Below limit.
Store value and time
of occurance
Time (days, weeks)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000698

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61B 5/02, A61N 1/365
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61B, A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Lazar Mandinov et al Diastolic Heart failure Cardiovascular Research vol 45, no 4 (2000) 813-825 AN NLM 10728407 see page 814-818 --	1-26
A	Daniel J. Lenihan et al Mechanisms, diagnosis, and treatment of diastolic heart failure vol. 130, no. 1, 1995 AN NLM 7611107 see page 157, column 2 - page 159, column 2 --	1-26

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2004	15 -12- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Bo Gustavsson/MN Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000698

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02053026 A2 (MEDTRONIC, INC), 11 July 2002 (11.07.2002), page 7, line 15 - page 8, line 11; page 22, line 14 - page 23, line 19; page 33, line 27 - page 37, line 25 ---	1-26
A	WO 0243587 A1 (ST.JUDE MEDICAL AB), 6 June 2002 (06.06.2002), see whole document --- --------	1-26

INTERNATIONAL SEARCH REPORT

International application No.
SE2004/00698

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-26
because they relate to subject matter not required to be searched by this Authority, namely:

See next page

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
SE2004/000698

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Claims 1826 relate to a method of treatment of the human body by surgery or by therapy/ a diagnostic methd pratised on the human or animal body/Rule 39.1(1v). Nevertheless a search has been executed for these claims. The search has been based on the alleged effects of the device.

INTERNATIONAL SEARCH REPORT
Information on patent family members

30/10/2004

International application No.
PCT/SE 2004/000698

WO	02053026	A2	11/07/2002	CA	2433359 A	11/07/2002
				EP	1347704 A	01/10/2003
				JP	2004523269 T	05/08/2004
				US	6738667 B	18/05/2004
				US	20030074029 A	17/04/2003
WO	0243587	A1	06/06/2002	EP	1339320 A	03/09/2003
				SE	0004417 D	00/00/0000
				US	20040049238 A	11/03/2004